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(54) **Camptothecin derivatives and process for preparing same.**

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CHEMICAL ABSTRACTS, vol. 90, no.13, 26th March 1979, page 34, column 2, abstract no. 97494h, Columbus, Ohio, US ; J.A. ADAMOVICS et al.: "Prodrug analogs of the antitumor alkaloid camptethecin"

PATENT ABSTRACTS OF JAPAN, vol. 11, no. 47 (C-403)(2494), 13th February 1987 & JP-A-61210032

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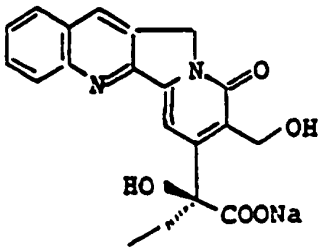
Description

The present invention relates to new camptothecin derivatives useful as anti-tumor agents or intermediates thereof and to a process for preparing such derivatives. More particularly, the present invention relates to new prodrug-type camptothecin derivatives which exhibit excellent anti-tumor activity in the living body with a low level of toxicity as well as a process for the preparation of the new camptothecin derivatives starting from 7-ethylcamptothecin.

Camptothecin is an alkaloid extracted and isolated from Camptotheca acuminata (Nyssaceae), which has a pentacyclic structure consisting of a characteristic fused 5-ring system consisting of quinoline (rings A and B), pyrroline (ring C), α-pyridone (ring D) and a six-membered lactone (ring E) and is distinguished by displaying a strong inhibitory activity towards biosynthesis of nucleic acid. In addition, camptothecin is a unique anti-tumor substance characterized by its rapid and reversible action and its lack of any cross-tolerance with the existing anti-tumor agents and by exhibiting a strong anti-tumor activity against experimentally transplanted carcinoma such as leukemia L-1210 in mice or Walker 256 sarcoma in rats. Although camptothecin is still regarded as one of the most potent substances possessing anti-tumor activity, the use of this compound itself for clinical treatments is significantly limited because of high toxicity. Moreover, camptothecin and the majority of derivatives thereof are sparingly soluble in water and thus involve a problem in case of administration as medicaments.

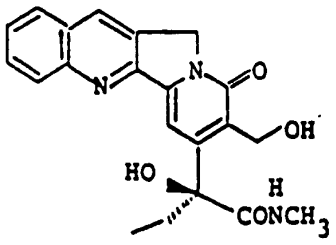
Accordingly, a number of attempts have been made not only to reduce toxicity of camptothecin while maintaining its anti-tumor activity by converting camptothecin chemically into its derivatives but also to make camptothecin and derivatives thereof easily soluble in water by chemical modifications of the camptothecin molecule or substituents therein. As one of such attempts, 10-hydroxy-substituted derivatives among the camptothecin derivatives having been prepared hitherto are of interest in that the 10-hydroxy-substituted derivatives maintain an excellent anti-tumor activity with reduced toxicity. However, the derivatives were found to be sparingly soluble in water and therefore cannot be used as medicament without difficulty. As a method for making camptothecin derivatives soluble in water, for example, a ring-opening reaction for the E-ring (lactone ring) of the camptothecin derivatives was used in the prior art to form an alkali metal salt of the carboxyl function. However, any chemical modification of the E-ring, including such ring-opening reaction, revealed only failure in maintaining anti-tumor activity and very poor improvement in toxicity [J. Med. Chem., 19, 675 (1976)].

According to a prior report, a water-soluble derivative of camptothecin of the formula (II) (hereinafter referred to as camptothecin sodium salt) obtainable by the treatment of the E-ring (the lactone moiety) of camptothecin with an aqueous sodium hydroxide solution is not found to be useful as anti-tumor agent because of its toxicity of causing e.g. myelosuppression or hemorrhagic cystitis constituting a dose limiting factor [Cancer Chemother. Rep., 54, 461 (1970)].

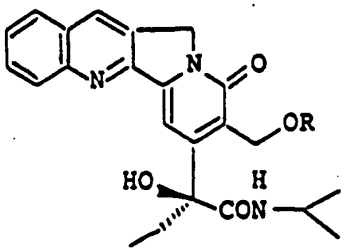


(II)

M. C. Wani et al. reported that the anti-tumor activity of the camptothecin sodium salt is reduced to a fraction of what is found in a derivative with the lactone form [M. C. Wani et al., J. Med. Chem., 23, 554 (1980)]. It has been believed since then that the E-ring (the lactone moiety) of camptothecin, including the 20-hydroxyl group, is an essential partial structure for camptothecin to exhibit its anti-tumor activity. Any of the few previous reports on the chemical modification of the E-ring (the lactone moiety) revealed that the derivatives obtained by such chemical modification exhibit only little or no anti-tumor activity. For example, an E-ring (lactone)-opened derivativ as th methylamide of th formula (III) shown below or as the isopropylamide of the formula (IV) shown below was reported to show very little or no activity [Th Alkaloids, ed. by A. Brossi, Academic Press, N.Y., 1983 and J. Med. Chem., 22, 310 (1979)].



(III)



(IV)

(wherein R is H, acetyl or propionyl.)

From the studies on various camptothecin derivatives prepared heretofore, it now becomes evident that chemical modifications in the E-ring, especially the E-ring opening, of camptothecin derivatives significantly adversely affect the anti-tumor activity. Under these circumstances, there is a great demand in this art for developing a new class of camptothecin derivatives maintaining strong anti-tumor activity even if chemically modified in the E-ring.

As a part of our studies on the preparation of water-soluble prodrug-type derivatives of camptothecin, we fixed our eyes on the E-ring of camptothecin derivatives to explore the possibility of converting them into a prodrug form. As the 17-hydroxy group of camptothecin in free form is spontaneously cyclized under neutral conditions with the partner carboxyl group to form a lactone ring, we have made extensive researches to solve simultaneously both problems of making the derivatives water-soluble and reconstructing the E-ring of the E-ring-opened derivatives in the living body after administration by masking the 17-hydroxy group of the E-ring-opened derivatives with such a protecting group as will be split off by hydrolysis by the action of an endogenous enzyme and converting the partner carboxyl group into a water-soluble carboxamide group.

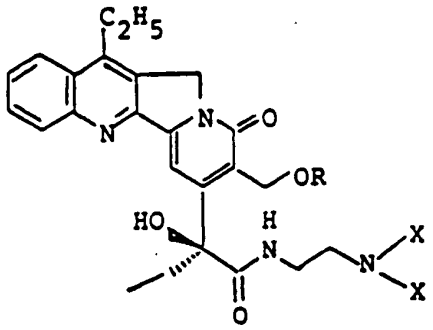
Accordingly, it is an object of the present invention to provide new prodrug-type camptothecin derivatives which exhibit excellent anti-tumor activity with a low level of toxicity.

It is another object of the present invention to provide new E-ring-opened camptothecin derivatives which are convertible into derivatives with the E-ring in the living body.

It is still another object of the present invention to provide a process for preparing water-soluble E-ring-opened camptothecin derivatives starting from 7-ethylcamptothecin.

As a result of our extensive researches made for developing new water-soluble camptothecin derivatives to achieve the above mentioned objects, we have succeeded in opening the E-ring of 7-ethylcamptothecin with an N,N-dialkylethylenediamine to obtain E-ring-opened carboxamide derivatives which can easily be converted in the living body into the derivatives having the corresponding E-ring.

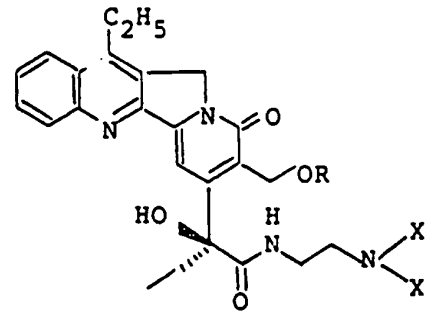
In accordance with one embodiment of the present invention there are provided new camptothecin derivatives of the general formula:



(I)

wherein X is a lower alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or branched unsubstituted C_1-C_{18} alkyl group; a lower alkyl group substituted by a halogen atom or a lower alkylthio, amino, acylamino, hydroxyl, lower alkoxy, phenoxy or naphthyloxy or lower alkoxycarbonyl group; a C_3-C_{19} alkenyl, C_3-C_{19} alkynyl or C_3-C_8 cycloalkyl group; a C_3-C_8 cycloalkyl group substituted by an acylamino-lower alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, lower alkoxycarbonyl, lower alkyl, phenyl or lower alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thienyl group, and their acid addition salts formed at the amino group and quaternary ammonium salts.

In accordance with another embodiment of the present invention, there is provided a process for the preparation of new camptothecin derivatives of the general formula:

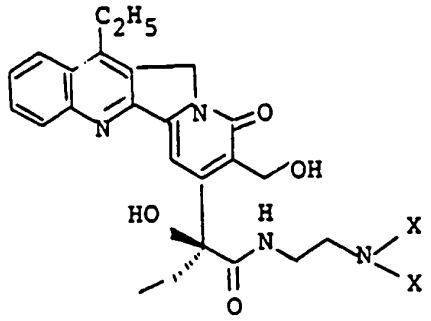


(I)

wherein X is a lower alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or branched unsubstituted C_1-C_{18} alkyl group; a lower alkyl group substituted by a halogen atom or a lower alkylthio, amino, acylamino, hydroxyl, lower alkoxy, phenoxy or naphthyloxy or lower alkoxycarbonyl group; a C_3-C_{19} alkenyl, C_3-C_{19} alkynyl or C_3-C_8 cycloalkyl group; a C_3-C_8cycloalkyl group substituted by an acylamino-lower alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, lower alkoxycarbonyl, lower alkyl, phenyl or lower alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thienyl group, and their physiologically acceptable acid-addition salts at the amino group, which comprises treating 7-ethylcamptothecin with an ethylenediamine derivative of the general formula:

$H_2N\text{-}CH_2CH_2\text{-}NX_2$ (VI)

wherein X has the same meaning as given above,
to form a 7-ethyl-17-hydroxymethylcamptothecin-21-(2-dialkylamino)ethylamide of the general formula:



(V)

wherein X has the same meaning as given above,
and if necessary, acylating the resultant compound of the general formula

Z-COY (VII)

wherein Y has the same meaning as given above and Z is a hydroxyl group, a halogen atom or the grouping -O-COY, and if desired, converting the resultant compound of the general formula (I) into its physiologically acceptable acid addition salt or quaternary ammonium salt or vice versa.

In the general formula (I) standing for the new compounds of this invention, the lower alkyl, alkoxy and alkylthio groups have 1-6, preferably 1-4 carbon atoms in the alkyl moiety. Thus, the term "lower" is to be interpreted as having 1-6 carbon atoms. These groups may be linear or branched in their alkyl moiety. Illustrative of the lower alkyl groups and the linear or branched unsubstituted C_1-C_{18} alkyl groups are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, hexadecyl and octadecyl. Examples of the lower alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, pentoxy, hexoxy. Examples of the lower alkylthio include alkylthio groups corresponding to the aforesaid alkoxy groups. Examples of the alkenyl groups with 3-19 carbon atoms include propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl,decenyl, undecenyl, dodecenyl, tetradecenyl, hexadecenyl, octadecenyl and nonadecenyl groups. Mentioned as the alkynyl groups with 3-19 carbon atoms are alkynyl groups corresponding to the aforesaid alkenyl groups. The acyl moiety in the acylamino and N-acylpyrrolidyl groups stands for a residue of an acid preferably selected from aliphatic and aromatic carboxylic acids including amino acids, aliphatic and aromatic sulfonic acids, and halogen- or hydroxy-substituted derivatives thereof.

In case the acyl group is derived from an amino acid, it may contain a protective group for the amino group. A preferable acyl moiety is, for example, a lower alkanoyl or benzoyl group which may be substituted.

Illustrative of the cycloalkyl groups are, for example, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups, with cyclopropyl, cyclopentyl and cyclohexyl being preferable.

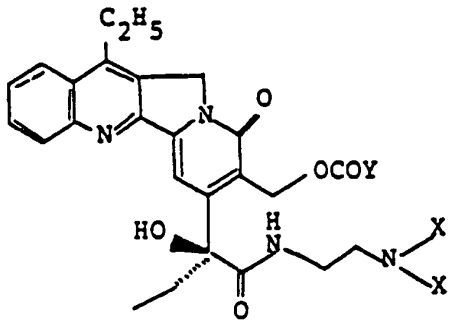
7-ethylcamptothecin used as the main starting material is commercially available or can be prepared according to the process disclosed in U.S. Patent Re. 32,518.

Preferable examples of the N,N-di(lower alkyl)-ethylenediamine used for opening the E-ring of 7-ethylcamptothecin include N,N-dimethyl-ethylenediamine, N,N-diethyl-ethylenediamine, N,N-dipropyl-ethylenediamine and N,N-dibutyl-ethylenediamine.

The process of this invention for preparing the new camptothecin derivatives comprises the two steps of treating 7-ethylcamptothecin with an N,N-di(lower alkyl)-ethylenediamine and optionally acylating the 17-hydroxyl group of the resultant compound with a compound of the general formula:

Z-COY (VII)

wherein Y and Z have the same meanings as given above, to obtain a compound of the general formula:



(VIII)

wherein X, Y and Z have the same meanings as given above.

In the first step for the treatment with an N,N-di(lower alkyl)-ethylenediamine, 7-ethylcamptothecin is dissolved in an excess amount of the N,N-di(lower alkyl)-ethylenediamine. As the excess amount of the N,N-di(lower alkyl)-ethylenediamine functions as a reaction solvent, there is generally no necessity of using a reaction solvent additionally. The solution is then stirred preferably in a nitrogen atmosphere for a period generally from 10 minutes to 5 hours, preferably from 30 minutes to 2 hours within the temperature range from room temperature to 100 °C, preferably from 30 to 70 °C. By raising the reaction temperature, the reaction time may be shortened accordingly. After completion of the reaction, the excess N,N-di(lower alkyl)-ethylenediamine is distilled off under reduced pressure. The residue is taken up in a solvent such as methylene chloride or chloroform and the solution is added to an inert solvent such as n-hexane in an amount of several times as much as the solution whereby the resultant compound is precipitated as crystals which are then collected by filtration. 7-Ethyl-17-hydroxycamptothecin-21-[2-di(lower alkyl)]amino ethylamide as an E-ring-opened product is thus obtained in a theoretical yield. This compound can be shown by the general formula (V) and can optionally be acylated in the 17-hydroxy position thereof. This compound reverts to the starting compound, 7-ethylcamptothecin, when allowed to stand in a solution thereof or subjected to column chromatography on silica gel.

In the subsequent step of the optional acylation, the reaction itself is carried out according to a usual manner for acylation of the hydroxyl group. The E-ring-opened camptothecin derivative of the general formula (V) is dissolved in a solvent and a catalytic amount of 4-N,N-dimethylaminopyridine is added to the solution. Illustrative of the solvent used for this acylation are, for example, methylene chloride, chloroform, DMF, dimethylsulfoxide and ether. The solution is stirred under cooling, preferably under ice-cooling and a compound of the general formula (VII) as acylating agent alone or in a solvent as above mentioned is added, and the mixture is continuously stirred under cooling or at room temperature until the reaction is completed. Water is then added to the reaction mixture and then an aqueous solution of caustic alkali, for example, 1N-NaOH solution, is added to the mixture to make it weakly alkaline. The resultant compound is extracted with methylene chloride or chloroform and the extract is washed with a saturated aqueous solution of edible salt. The organic phase is then dried over magnesium sulfate or sodium sulfate and then concentrated under reduced pressure until dryness. The residue is then subjected to column chromatography on silica gel whereby a 17-acylated compound of the general formula (VIII) is obtained in a moderate yield.

Alternatively, the 17-acylated compound can be obtained by treating a compound of the general formula (VII) with a condensing agent such as dicyclohexylcarbodiimide or the like mild dehydrating agent and then reacted with the E-ring-opened compound of the general formula (V) in the presence of N,N-dimethylaminopyridine, and can be purified in the same manner as described above.

The compounds of this invention represented by the general formula (I) can be converted, if desired, into physiologically acceptable acid addition salts or quaternary salts thereof with proper inorganic or organic acids or alkyl or aryl halides, respectively. Examples of the inorganic and organic acids used for the preparation of acid addition salts include hydrohalic acids such as hydrochloric acid, sulfuric acid, methanesulfonic acid, alkanoic acids such as acetic acid, and alkanedicarboxylic acids such as tartaric acid, citric acid, etc. Preferable examples of the alkyl halide include methyl iodide and ethyl bromide. In order to prepare th se salts, the compound of the general formula (I) is incorporated with the acid or the alkyl halide in an equimolar amount and then the mixtur is heated until dryn ss or lyophilized. Th acid addition salts can be liberated by the treatment with an alkaline substance.

The acid addition salts are formed at the amino group of the ethylenediamine moiety and the quaternary salts are formed at the tertiary amino group.

The new camptothecin derivatives of this invention are useful as medicaments or intermediates therefore. A recommended dose of the derivatives is generally 1-400 mg/kg of body weight in case of rat.

The present invention will now be illustrated in more detail by way of examples.

Example 1

(Preparation of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylammino)ethylamide)

7-Ethylcamptotecin(1.00g, 2.66mmol) was stirred in N,N-dimethylethylenediamine(20ml) for an hour at 50°C under a N_2 atmosphere. After the stirring, the reaction mixture was evaporated to dryness under reduced pressure. The remaining solid was dissolved in dichloromethane, and the solution was poured into n-hexane(300ml). The precipitated crystals were filtrated by suction, whereupon the title compound was obtained(0.87g, 70.7% in yield) as yellow cristals.
m.p. 195~215 °C

Example 2

(Preparation of 7-ethyl-17-acetoxycamptothecin-21-(2-diethylamino)ethylamide)

(a) 7-Ethylcamptothecin(1.00g, 2.66mmol) was dissolved in N,N-diethyl-ethylenediamine(20ml), the reaction followed by the after-treatment was carried out in the same manner as described in Example 1, whereby 7-ethyl-17-hydroxycamptothecin-21-(2-diethylamino)ethylamide was obtained.

(b) Acetyl chloride(173μl, 2.44mmol) was added to the ice-cooled solution of 7-ethyl-17-hydroxycamptothecin-21-(2-diethylamino)ethyl amide, obtained by step(a), in dichloromethane(20ml), in the presence of 4-dimethylaminopyridine(100mg, 0.82mmol). After stirring for an hour under ice-cooling, water was added to the reaction mixture, and the aqueous phase was adjusted to weak basic conditions by adding 1N NaOH. After shaking, the organic phase was separated, washed with saturated aqueous solution of NaCl, dried over anhydrous $MgSO_4$, filtered, and then evaporated to dryness under reduced pressure. The residual material was purified through silica gel column chromatography with $CHCl_3$-MeOH as an eluent and crystallized from n-hexane to give the title compound as pale yellow crystals.
m.p. 177~181 °C

Example 3

(Preparation of 7-ethyl-17-benzoyloxycamptothecin-21-(2-diethylamino) ethylamide)

Using benzoyl chloride(311μl, 2.44mmol) as an acid chloride in place of acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby the title compound was obtained as yellow crystals. m.p. 151~164 °C IR$_\nu$ (KBr)cm^{-1};3350, 2930, 1700, 1650, 1590, 1510, 1450, 1270, 1100, 710.

Example 4

(Preparation of 7-ethyl-17-propionyloxycamptothecin-21-(2-diethylamino) ethylamide)

Using propionyl chloride(212μl, 2.44mmol) as an acid chloride in place of acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby the title compound was obtained as pale yellow crystals. m.p. 208~209.5 °C IR$_\nu$ (KBr)cm^{-1};3360, 2960, 1730, 1650, 1590, 1520, 1460, 1180, 760.

Example 5

(Preparation of 7-ethyl-17-butyryloxycamptothecin-21-(2-diethylamino) ethylamide)

Using butyryl chloride(253μl, 2.44mmol) as an acid chloride in place of acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby

the title compound was obtained as pale yellow crystals.
m.p. 150~154 °C
IR ν (KBr)cm^{-1}; 3370, 2960, 1730, 1650, 1590, 1520, 1180, 760.

Example 6

(Preparation of 7-ethyl-17-butyryloxycamptothecin-21-(2-dimethylamino) ethylamide)

Using 21-(2-dimethylamino)ethylamide derivative and butyryl chloride(269$\mu\ell$, 2.59mmol) in place of 21-(2-diethylamino)ethylamide derivative and acetyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 2(b), whereby the title compound was obtained as pale yellow crystals.
m.p. 164.5~166.5 °C
IR ν (KBr)cm^{-1}; 3370, 2960, 1730, 1650, 1590, 1520, 1460, 1180, 760.

Example 7

(Preparation of 7-ethyl-17-benzoyloxycamptothecin-21-(2-dimethylamino) ethylamide)

Using benzoyl chloride(331$\mu\ell$, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(142mg, 11.6% in yield).
m.p. 172~176 °C
IR ν (KBr)cm^{-1}; 3350, 2980, 1710, 1640, 1590, 1500, 1450, 1270, 1100, 715.
NMR(in $CDCl_3$) δ ppm; 1.09(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.35(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.18(6H, s, -N-$(\underline{CH_3})_2$), 2.34~2.41(3H, m, -$CH_2\underline{CH_2}$N= and 20-$\underline{CH}H'\underline{CH_3}$), 2.44~2.51(1H, m, 20-$CH\underline{H}'\underline{CH_3}$), 3.08~3.14(2H, m, 7-$\underline{CH_2}CH_3$), 3.19~3.25(1H, m, -NHC$\underline{H}H'CH_2$N=), 3.32~3.39(1H, m, -NHC$H\underline{H}'CH_2$N=), 5.15(2H, dd, J=18.7Hz, 5-H_2), 5.76 and 5.87(two 1H's, d, J=11.7Hz, 17-H_2), 7.35~7.39(3H, m, 17-O(C=O)Ph and -NH$\underline{CH_2}CH_2$N=), 7.50(1H, t, J=7.3Hz, 17-O(C=O)Ph), 7.55(1H, t, J= 7.3Hz, 10-H), 7.63(1H, s, 14-H), 7.73-(1H, t, J=7.0Hz, 11-H), 7.93(1H, d, J=8.4Hz, 9-H), 8.03(2H, d, J=7.3Hz, 17-O(C=O)Ph), 8.13(1H, d, J=8.4Hz, 12-H).

Example 8

(Preparation of 7-ethyl-17-(4-methoxybenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-methoxybenzoyl chloride(363$\mu\ell$, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(224mg, 17.4% in yield).
m.p. 176~177.5 °C
IR ν (KBr)cm^{-1}; 3400, 3300, 2960, 1690, 1660, 1640, 1600, 1500, 1450, 1260, 1240, 1160, 1090, 760.
NMR(in $CDCl_3$) δ ppm; 1.08(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.36(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.24(6H, s, -N-$(\underline{CH_3})_2$), 2.36~2.49(4H, m, -$CH_2\underline{CH_2}$N= and 20-$\underline{CH_2}CH_3$), 3.12(2H, q, 7-$\underline{CH_2}CH_3$), 3.21~3.27 and 3.37~3.42-(two 1H's, m, -NHC$\underline{H_2}CH_2$N=), 3.82(3H, s, -$\underline{OCH_3}$), 5.17(2H, dd, 5-$\underline{H_2}$), 5.70 and 5.85(two 1H's, d, J=11.7Hz, 17-H_2), 6.85(2H, d, J=8.8Hz, Arom), 7.57(1H, t, 10-H), 7.64(1H, s, 14-H), 7.74 (1H, t, 11-H), 7.96~8.00(3H, m, 9-H and Arom), 8.15(1H, d, 12-H).

Example 9

(Preparation of 7-ethyl-17-(4-fluorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-fluorobenzoyl chloride(305$\mu\ell$, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(613mg, 48.5% in yield).
m.p. 167.2~169.5 °C
IR ν (KBr)cm^{-1}; 3400, 2970, 1710, 1650, 1600, 1500, 1455, 1270, 1110, 765.
NMR(in $CDCl_3$) δ ppm; 1.14(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.27(3H, t, J=7.3Hz, 7-$CH_2\underline{CH_3}$), 2.17(6H, s, -N-$(\underline{CH_3})_2$), 2.32~2.44(3H, m, $CH_2\underline{CH_2}$N= and 20-$\underline{CH}H'\underline{CH_3}$), 2.57~2.64(1H, m, 20-$CH\underline{H}'\underline{CH_3}$), 2.89~3.01(2H, m,

7-CH_2CH_3), 3.07~3.15 and 3.33~3.41(two 1H's, m, -NHC$H_2$$CH_2$N=), 4.97(2H, dd, J=18.3Hz, 5-H_2), 5.80-(2H, d, J=11.7Hz, 17-H_2), 7.00(2H, t, J=8.8Hz, Arom), 7.35(1H, t, J=7.3Hz, 10-H), 7.59 (1H, s, 14-H), 7.61-(1H, d, 9-H), 7.70(1H, t, 11-H), 7.94(1H, d, J=8.1Hz, 12-H), 8.02(2H, dd, Arom).

Example 10

(Preparation of 7-ethyl-17-(4-bromobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-bromobenzoyl chloride(568mg, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(926mg, 66.4% in yield).
m.p. 176~179.5 °C
IR ν (KBr)cm^{-1}; 3350, 2980, 1710, 1670, 1650, 1595, 1510, 1450, 1270, 1095, 760.
NMR(in $CDCl_3$) δ ppm; 0.95(3H, t, J=7.3Hz, 20-CH_2CH_3), 1.30(3H, t, J=7.3Hz, 7-CH_2CH_3), 2.39~2.48(2H, m, 20-CH_2CH_3), 2.77(6H, s, -$N(CH_3)_2$), 2.99~3.22(4H, m, -CH_2CH_2N= and 7-CH_2CH_3), 3.36~3.44 and 3.88~3.93(two 1H's, m, -NHC$H_2$$CH_2$N=), 5.09(2H, dd, J=19.1Hz, 5-H_2), 5.76(2H, dd, J=11.7Hz, 17-H_2), 7.41 (2H, d, Arom), 7.54(1H, t, 10-H), 7.75~7.79(2H, m, 14-H and 11-H), 7.92(1H, d, 9-H), 8.05(1H, d, 12-H), 8.20(1H, br, -NHC$H_2$$CH_2$N=).

Example 11

(Preparation of 7-ethyl-17-(2-bromobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 2-bromobenzoyl chloride(568mg, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(324mg, 24.5% in yield).
m.p. 180~183.5 °C
IR ν (KBr)cm^{-1}; 3380, 3250, 2980, 1710, 1670, 1595, 1510, 1460, 1240, 1140, 1100, 940.
NMR(in $CDCl_3$) δ ppm; 1.14(3H, t, J=7.3Hz, 20-CH_2CH_3), 1.31(3H, t, J=7.3Hz, 7-CH_2CH_3), 2.16(6H, s, -N-$(CH_3)_2$), 2.29~2.41(3H, m, -CH_2CH_2N= and 20-CHH'CH_3), 2.54~2.63(1H, m, 20-CHH'CH_3), 2.94~3.19(3H, m, 7-CH_2CH_3 and -NHCHH'CH_2N=), 3.32~3.38(1H, m, -NHCHH'CH_2N=), 5.05(2H, dd, J=19.1Hz, 5-H_2), 5.80(2H, s, 17-H_2), 7.41 (1H, t, 10-H), 7.46~7.49(2H, m, Arom), 7.54(1H, t, -NH-), 7.58 (1H, s, 14-H), 7.65(1H, t, 11-H), 7.71(1H, d, 9-H), 7.84~7.87(2H, m, Arom), 8.00 (1H, d, J=7.3Hz, 12-H).

Example 12

(Preparation of 7-ethyl-17-propionyloxycamptothecin-21-(2-dimethylamino)ethylamide)

Using propionyl chloride(225$\mu\ell$, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 6, whereby the title compound was obtained as pale yellow crystals(535mg, 47.7% in yield).
m.p. 137~154 °C
IR ν (KBr)cm^{-1}; 3360, 2970, 1760, 1730, 1650, 1595, 1510, 1460, 1170, 1130, 1070.
NMR(in $CDCl_3$) δ ppm; 1.12(6H, t, J=7.3Hz, 20-CH_2CH_3 and 17-O(C=O)CH_2CH_3), 1.30(3H, t, J=7.3Hz, 7-CH_2CH_3), 2.26(6H, s, -$N(CH_3)_2$), 2.28~2.37(3H, m, CH_2CH_2N= and 20-CHH'CH_3), 2.42~2.56(3H, m, 20-CHH'CH_3 and 17-O(C=O)CH_2CH_3), 2.91~3.06(2H, m, 7-CH_2CH_3), 3.25~3.33 and 3.43~3.51(two 1H's, m, -NHC$H_2$$CH_2$N=), 4.99(2H, dd, J=18.3Hz, 5-H_2), 5.49(2H, d, J=11.7Hz, 17-H_2), 7.41(1H, t, 10-H), 7.53(1H, s, 14-H), 7.65(1H, t, 11-H), 7.71(1H, d, 9-H), 7.99(1H, d, 12-H).

Example 13

(Preparation of 7-ethyl-17-(4-chlorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

Using 4-chlorobenzoyl chloride(329$\mu\ell$, 2.59mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in th same mann r as described in xample 6, whereby the title compound was obtained as pale yellow crystals(613mg, 47.2% in yield).
m.p. 167~188 °C
IR ν (KBr)cm^{-1}; 3360, 2970, 1710, 1670, 1650, 1590, 1510, 1450, 1280, 1090.

Example 14

(Preparation of 7-ethyl-17-(4-nitrobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its methanesulfonate)

To the ice-cooled solution of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylamino)ethylamide(1.00g, 2.15mmol) in dichloromethane(20ml), 4-N,N-dimethylaminopyridine(100mg, 0.82mmol) and 4-nitrobenzoyl chloride(1.20g, 6.45mmol) were added. After stirring under ice-cooling for an hour, the reaction mixture was dilluted with dichloromethane, washed with a saturated aqueous solution of $NaHCO_3$ and with a saturated aqueous solution of NaCl. The organic phase was separated, dryed over anhydrous $MgSO_4$, filtered, and then evaporated to dryness under reduced pressure. The residual material was purified through silica gel column chromatography with $CHCl_3$ -MeOH as an eluent and crystallized from $CHCl_3$ -n-hexane to give the title compound(633mg, 47.9% in yield) as pale yellow powder.
m.p. 153~158 °C (dec.)
IR ν (KBr)cm^{-1}; 3380, 2960, 2940, 1717, 1650, 1580, 1525, 1270.
NMR($CDCl_3$) δ ppm; 1.13(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.35(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.16(6H, s, -N-$(CH_3)_2$), 2.27~2.61(4H, m, -$CH_2\underline{CH_2}N$= and 20-$\underline{CH_2}CH_3$), 3.00~3.39(4H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}N$=), 5.13(2H, dd, J=19.1Hz, 5-H_2), 5.36(1H, br, 20-OH), 5.85(2H, dd, J=11.7Hz, 17-H_2), 7.37-(1H, br-t, J=5.1Hz, $\underline{NH}CH_2CH_2N$=), 7.51(1H, t, 10-H), 7.59(1H, s, 14-H), 7.71(1H, t, 11-H), 7.86(1H, d, 9-H), 8.09(1H, d, 12-H), 8.15~8.25(4H, m, -C_6H_4-p-NO_2).

Methanesulfonate

To the $CHCl_3$ solution of free compound(200mg, 0.33mmol) a 0.1M THF solution of methanesulfonic acid(5.0ml) was added. Then n-hexane (20ml) was added to the solution and the resulting precipitated crystals were filtrated and dried to give yellow crystals of methanesulfonate in quantitative yield.
IR ν (KBr)cm^{-1}; 3380, 2685, 1715, 1650, 1605, 1520, 1270, 1200.
NMR(DMSO-d_6) δ ppm; 0.92(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.18~2.29(2H, m, 20-$\underline{CH_2}CH_3$), 2.31(3H, s, $\underline{CH_3}SO_3^-$), 2.74 and 2.75(two 3H's, s, $NH^+(CH_3)_2$), 3.01~3.50(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.36(2H, s, 5-$H_2$), 5.70(2H, dd, J=11.0Hz, 17-H_2), 6.35~6.49(1H, br, 20-OH), 7.53-(1H, s, 14-H), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 8.14 and 8.36(two 2H's, d, J=8.8Hz, -C_6H_4-p-NO_2), 8.20-(1H, d, 9-H), 8.33(1H, d, 12-H), 8.47(1H, t, J=5.9Hz, -$\underline{NH}CH_2CH_2NH^+$=), 9.14~9.34(1, br, -$NH^+$=).

Example 15

(Preparation of 7-ethyl-17-(4-trifluoromethylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide, its methanesulfonate, and hydrochloride)

Using 4-trifluoromethylbenzoyl chloride(1.35g, 6.45mmol) as an acid chloride in place of 4-nitrobenzoyl-chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a pale yellow solid of the title compound(916 mg, 66.9% in yield) was obtained.
m.p. 144~148 °C (dec.)
IR ν (KBr)cm^{-1}; 3360, 2960, 2930, 1715, 1650, 1595, 1510, 1325, 1275, 1165, 1125, 1100.

Methanesulfonate

To the $CHCl_3$ solution of free compound(200mg) a 0.1M THF solution of methanesulfonic acid(4.7ml) was added. Then n-hexane(20ml) was added to the solution and the resulting precipitated crystals were collected by filtration and dried to give yellow crystals of methanesulfonate in quantitative yield.
IR ν (KBr)cm^{-1}; 3380, 2670, 1715, 1650, 1610, 1325, 1275, 1195, 1120, 1055.
NMR(DMSO-d_6) δ ppm; 0.91(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.24(2H, q, 20-$\underline{CH_2}CH_3$), 2.34(3H, s, $\underline{CH_3}SO_3^-$), 2.74 and 2.75(two 3H's, s, $NH^+(CH_3)_2$), 3.04~3.49(6H, m, 7-$\underline{CH_2}CH_3$ and -$NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.35(2H, s, 5-$H_2$), 5.69(2H, dd, J=11.0Hz, 17-H_2), 6.22~6.60(1H, br, 20-OH), 7.54(1H, s, 14-H), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 7.91 and 8.11(two 2H's, d, -C_6H_4-p-CF_3),8.20(1H, d, 9-H), 8.31-(1H, d, 12-H, 8.47(1H, t, J=5.9Hz, $\underline{NH}CH_2CH_2NH^+$=), 9.17~9.37(1H, br, -$NH^+$=).

Hydrochloride

To the suspension of free compound(200mg) in distilled water(5ml) 0.1N HCl(3.8ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3360, 2670, 1715, 1650, 1595, 1510, 1325, 1275, 1120, 1100.
NMR(DMSO-d_6) δ ppm; 0.89(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.26(2H, q, 20-$\underline{CH_2}CH_3$), 2.72 and 2.73(two 3H's, s, $NH^+=(CH_3)_2$), 3.00 ~3.56(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+=$), 5.34(2H, s, 5-$H_2$), 5.71(2H, dd, J=11.0Hz, 17-H_2), 6.35~6.70(1H, br, 20-OH), 7.57(1H, s, 14-H), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 7.91 and 8.10(two 2H's, d, -C_6H_4-p-CF_3), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H), 8.48-(1H, t, J=5.9Hz, -$\underline{NH}CH_2CH_2NH^+=$), 9.90~10.10(1H, br, -$NH^+=$).

Example 16

(Preparation of 7-ethyl-17-(4-iodobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its methanesulfonate)

Using 4-iodobenzoyl chloride (1.00g, 3.75mmol) as an acid chloride in place of 4-nitrobenzoyl chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a pale yellow solid of the title compound(648mg, 43.2% in yield) was obtained.
m.p. 146~150 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2960, 2930, 1710, 1650, 1585, 1510, 1270, 1100.

Methanesulfonate

To the $CHCl_3$ solution of free compound(200mg) a 0.1M THF solution of methanesulfonic acid(4.2ml) was added. Then n-hexane(20ml) was added to the solution and the resulting precipitated crystals were filtrated and dried to give yellow crystals of methanesulfonate in quantitative yield.
IR ν (KBr)cm^{-1}; 3360, 2670, 1710, 1650, 1610, 1585, 1270, 1195, 1055.
NMR(DMSO-d_6) δ ppm; 0.90(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.23(2H, m, 20-$\underline{CH_2}CH_3$), 2.33(3H, s, $\underline{CH_3}SO_3^-$), 2.74 and 2.75(two 3H's, s, $NH^+(CH_3)_2$), 3.02~3.48(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+=$), 5.35(2H, s, 5-$H_2$), 5.61(2H, dd, J=11.0Hz, 17-H_2), 6.24~6.55(1H, br, 20-OH, 7.52-(1H, s, 14-H), 7.66 and 7.91(two 2H's, d, $C_6\underline{H_4}$-p-I), 7.75(1H, t, 10-H), 7.87(1H, t, 11-H), 8.19(1H, d, 9-H), 8.30(1H, d, 12-H), 8.45(1H, t, J=5.5Hz, $\underline{NH}CH_2CH_2NH^+=$), 9.19~9.35(1H, br, -$NH^+=$).

Example 17

(Preparation of 7-ethyl-17-(1-naphthoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 1-naphthoyl chloride(615mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(371mg, 27.9% in yield) were obtained.
m.p. 144~147 °C (dec.)
IR ν (KBr)cm^{-1}; 3380, 2960, 2925, 1705, 1650, 1595, 1510, 1275, 1240, 1195, 1135.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.9ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (193mg, 91.0% in yield).
IR ν (KBr)cm^{-1}; 3380, 1700, 1650, 1590, 1510, 1275, 1240, 1195, 1135.
NMR(DMSO-d_6) δ ppm; 0.90(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.29(2H, q, 20-$\underline{CH_2}CH_3$), 2.70 and 2.71(two 3H's, s, $NH^+=(CH_3)_2$), 3.04 ~3.57(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+=$), 5.35(2H, s, 5-$H_2$), 5.74(2H, dd, J= 11.0Hz, 17-H_2), 6.40~6.60(1H, br, 20-OH), 7.51~7.71(4H, m, 14-H and Napht), 7.73(1H, t, 10-H), 7.86(1H, t, 11-H), 7.97~8.09(2H, m, Napht) 8.12~8.23(2H, m, 9-H and Napht), 8.29(1H, d, 12-H), 8.48(1H, t, J=5.5Hz, $\underline{NH}CH_2CH_2NH^+=$), 8.83 (1H, d, J=8.4Hz, Napht), 9.98~10.12(1H, br, $NH^+=$).

Example 18

(Preparation of 7-ethyl-17-(2-naphthoyloxy)camptothecin-21-(2-dimethylamino)ethylamid and its hydrochloride)

Using 2-naphthoyl chloride(615mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(538mg, 40.4% in yield) were obtained.
m.p. 179~183 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2970, 2930, 1700, 1650, 1590, 1510, 1455, 1275, 1220, 1195.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.9ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3380, 1705, 1650, 1595, 1280, 1225, 1195.
NMR(DMSO-d_6) δ ppm; 0.92(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.18~2.40(2H, q, 20-$\underline{CH_2}CH_3$), 2.70 and 2.71(two 3H's, s, $\underline{NH^+}(CH_3)_2$), 3.02~3.57(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.34(2H, s, 5-$H_2$), 5.74(2H, dd, J=11.0Hz, 17-H_2), 6.25~6.80(1H, br, 20-OH), 7.55~7.70-(3H, m, 14-H and Napht), 7.74(1H, t, 10-H), 7.87(1H, t, 11-H), 7.92~8.13(4H, m, Napht), 8.21(1H, d, 9-H), 8.29(1H, d, 12-H), 8.50(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+$=), 8.56(1H, s, Napht), 10.16~10.34(1H, br, NH^+=).

Example 19

(Preparation of 7-ethyl-17-(2-furoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 2-furoyl chloride(422mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(662mg, 55.1% in yield) were obtained.
m.p. ~ 151 °C (dec.)
IR ν (KBr)cm^{-1}; 3380, 1710, 1650, 1595, 1295, 1175, 1115.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.3ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3300, 2950, 1710, 1650, 1600, 1510, 1470, 1295, 1175, 1110.
NMR(DMSO-d_6) δ ppm; 0.87(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.10~2.35(2H, m, 20-$\underline{CH_2}CH_3$), 2.72 and 2.73(two 3H's, s, $\underline{NH^+}(CH_3)_2$), 3.04~3.64(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.31(2H, s, 5-$H_2$), 5.64(2H, dd, J=11.0Hz, 17-H_2), 6.28~6.66(1H, br, 20-OH), 6.66(1H, dd, J=1.8 and 3.3Hz, Furano), 7.20(1H, d, Furano), 7.57(1H, s, 14-H), 7.73(1H, t, 10-H), 7.86(1H, t, 11-H), 7.94(1H, d, Furano), 8.19(1H, d, 9-H), 8.28(1H, d, 12-H), 8.45(1H, t, J=5.5 Hz, -$\underline{NH}CH_2CH_2NH^+$=), 10.22~10,42(1H, br, NH^+=).

Example 20

(Preparation of 7-ethyl-17-(2-thenoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 2-thenoyl chloride(474mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(480mg, 38.8% in yield) were obtained.
m.p. 149~155 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2970, 2960, 1695, 1645, 1595, 1515, 1260, 1090.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.2ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3370, 2670, 1695, 1645, 1590, 1520, 1260, 1090.
NMR(DMSO-d_6) δ ppm; 0.88(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.7Hz, 7-CH_2 $\underline{CH_3}$), 2.13~2.38(2H, m, 20-$\underline{CH_2}CH_3$), 2.72 and 2.74(two 3H's, s, $NH^+(CH_3)_2$), 3.04~3.67(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+$=), 5.32(2H, s, 5-$H_2$), 5.66(2H, s, 17-$H_2$), 6.20~6.74(1H, br, 20-OH), 7.68~7.79(1H, m, Thiopheno), 7.59(1H, s, 14-H), 7.67~7.80(2H, m, 10-H and Thiopheno), 7.86(1H, t, 11-H), 7.91(1H, d, J=5.1Hz, Thiopheno), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.46(1H, t, J=5.5Hz, $\underline{NH}CH_2CH_2NH^+$=), 10.16~10.35(1H, br, NH^+=).

Example 21

(Preparation of 7-ethyl-17-cyclopropanecarbonyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using cyclopropanecarbonyl chloride(338mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(216mg, 18.8% in yield) were obtained.
m.p. 147~150 °C (dec.)
IR ν (KBr)cm^{-1}; 3375, 2965, 2930, 1715, 1645, 1595, 1515, 1455, 1395, 1175.

Hydrochloride

To the suspension of free compound(150mg) in distilled water(15ml) 0.1N HCl(3.4ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3370, 2670, 1710, 1645, 1595, 1515, 1395, 1175.
NMR(DMSO-d_6) δ ppm; 0.74~0.97(7H, m, 20-$CH_2\underline{CH_3}$ and cyclo-Pr), 1.33(3H, t, J= 7.3Hz, 7-$CH_2\underline{CH_3}$), 1.52~1.62(1H, m, cyclo-Pr), 2.10~2.31(2H, m, 20-$\underline{CH_2}CH_3$), 2.76 and 2.77(two 3H's, s, $NH^+(CH_3)_2$), 3.05~3.35(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+$=), 5.32(2H, s, 5-$H_2$), 5.37(2H, d, J=11.0Hz, 17-H_2), 6.28~6.58 (1H, br, 20-OH), 7.54(1H, s, 14-H), 7.74(1H, t, 10-H), 7.86(1H, t, 11-H), 8.19(1H, d, 9-H), 8.30(1H, d, 12-H), 8.40(1H, t, J=5.1Hz, -$\underline{NH}CH_2CH_2NH^+$=), 10.08~10.28 (1H, br, NH^+=).

Example 22

(Preparation of 7-ethyl-17-(3-fluorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 3-fluorobenzoyl chloride(512mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound (348mg, 27.6% in yield) were obtained.
m.p. 132~138 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2970, 2930, 1715, 1650, 1590, 1510, 1445, 1275, 1200.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3380, 2670, 1710, 1650, 1590, 1510, 1445, 1275, 1200.
NMR(DMSO-d_6) δ ppm; 0.89(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.3Hz, 7-CH_2 $\underline{CH_3}$), 2.26(2H, q, 20-$\underline{CH_2}CH_3$), 2.72 and 2.74(two 3H's, s, $NH^+(CH_3)_2$), 3.05~ 3.31(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}CH_2NH^+$=), 5.34(2H, s, 5-$H_2$), 5.68(2H, dd, J= 11.0Hz, 17-H_2), 6.38~6.60(1H, br, 20-OH), 7.46~7.67(4H, m, 14-H and Arom), 7.70~7.80(2H, 10-H and Arom), 7.87(1H, t, 11-H), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H), 8.48(1H, t, J=5.5Hz, -$NH\underline{CH_2}CH_2NH^+$=), 10.01~10.21(1H, -$\underline{NH}CH_2CH_2NH^+$=).

Example 23

(Preparation of 7-ethyl-17-(2-fluorobenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 2-fluorobenzoyl chloride(512mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(445mg, 35.2% in yield) were obtained.
m.p. 154~160 °C (dec.)
IR ν (KBr)cm^{-1}; 3360, 2960, 2930, 1715, 1650, 1610, 1510, 1450, 1295, 1250.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3360, 2670, 1710, 1650, 1610, 1515, 1450, 1295, 1250, 1220, 1120, 1080.
NMR(DMSO-d_6) δ ppm; 0.87(3H, t, J=7.0Hz, 20-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.7Hz, 7-CH_2 $\underline{CH_3}$), 2.18~2.33(2H, m, 20-$\underline{CH_2}CH_3$), 2.73 and 2.74(two 3H' s, s, $NH^+(CH_3)_2$), 3.05~3.60(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+=$), 5.32(2H,s, 5-$H_2$), 5.67(2H, dd, J=11.0Hz, 17-H_2), 6.36~6.60(1H, br, 20-OH), 7.23~7.38-(2H, m, Arom), 7.57(1H, s, 14-H), 7.60~7.69(1H, m, Arom), 7.74(1H, t, 10-H), 7.78~7.92(2H, m, 11-H and Arom), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.46(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+=$), 10.04~10.26(1H, -$NHCH_2CH_2\underline{NH}^+=$).

Example 24

(Preparation of 7-ethyl-17-(trans-4-benzyloxycarbonylaminomethylcyclohexanecarbonyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using trans-4-benzyloxycarbonylaminomethylcyclohexanecarbonyl chloride(2.00g, 6.46mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(1.00g, 31.6% in yield) were obtained.
m.p. ~ 112 °C (dec.)
IR ν (KBr)cm^{-1}; 3310, 2925, 1715, 1650, 1595, 1510, 1450, 1250, 1170, 1140.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(2.9ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3280, 2920, 2590, 1710, 1650, 1600, 1510, 1450, 1235, 1170, 1140.
NMR(DMSO-d_6) δ ppm; 0.74~0.98(5H, m, 20-$CH_2\underline{CH_3}$ and cyclo-Hex), 1.18~1.43 (6H, m, 7-$CH_2\underline{CH_3}$ and cyclo-Hex), 1.61~1.78(2H, m, cyclo-Hex), 1.81~1.98 (2H, m, cyclo-Hex), 2.08~2.28(3H, m, 20-$\underline{CH_2}\underline{CH_3}$ and cyclo-Hex), 2.75 and 2.76(two 3H's, s, $NH^+(CH_3)_2$), 2.83(2H, t-like, cyclo-Hex-$\underline{CH_2}NHCO_2CH_2Ph$), 3.05~3.63(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+=$), 4.98(2H, s, $CO_2\underline{CH_2}Ph$), 5.30 (2H, s, 5-H_2), 5.34(2H, dd, J=11.0Hz, 17-H_2), 6.37(1H, s, 20-OH), 7.23(1H, t, cyclo-Hex-$CH_2\underline{NH}CO_2CH_2Ph$), 7.25~7.40(5H, m, Ph), 7.55(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.37(1H, t, J=5.5 Hz, -$\underline{NH}CH_2CH_2NH^+=$), 9.98~10.14(1H, br, -$NHCH_2CH_2\underline{NH}^+=$).

Example 25

(Preparation of 7-ethyl-17-crotonyloxycamptothecin-21-(2-dimethylamino) ethylamide and its hydrochloride)

Using crotonyl chloride(337mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of th title compound(230mg, 20.1% in yield) were obtained.
m.p. 147~148 °C (dec.)
IR ν (KBr)cm^{-1}; 3355, 2970, 2960, 1710, 1650, 1595, 1510, 1180.

Hydrochloride

To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(3.6ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochlorid as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3380, 2670, 1705, 1650, 1595, 1515, 1180.
NMR(DMSO-d_6) δ ppm; 0.86(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-CH_2 $\underline{CH_3}$), 1.85(3H, d, J=7.0Hz, CH=$CH\underline{CH_3}$), 2.21(2H, q, 20-$\underline{CH_2}CH_3$), 2.75 and 2.76(two 3H's, s, $NH^+(CH_3)_2$), 3.03~3.60(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.30(2H, s, 5-$H_2$), 5.42(2H, dd, J=11.0Hz, 17-H_2), 5.85(1H, d, J=15.4Hz, $\underline{CH}$=CH-CH_3), 6.25~6.58(1H, br, 20-OH), 6.87(1H, dq, CH=$\underline{CH}CH_3$), 7.54(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.18(1H, d, 9-H), 8.28(1H, d, 12-H), 8.39(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+$=), 10.13~10.31(1H, br, -$NHCH_2CH_2NH^+$=).

Example 26

(Preparation of 7-ethyl-17-caproyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using caproyl chloride(435mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(226mg, 18.7% in yield) were obtained.
m.p. 134~137 °C (dec.)
IR ν (KBr)cm^{-1}; 3360, 2925, 1725, 1645, 1590, 1510, 1455, 1170.

Hydrochloride

To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(3.4ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3370, 2950, 2670, 1720, 1650, 1595, 1510, 1455, 1170.
NMR(DMSO-d_6) δ ppm; 0.72~0.98(6H, m, 20-$CH_2\underline{CH_3}$ and $CH_2(CH_2)_3\underline{CH_3}$), 1.17~ 1.61(9H, m, 7-$CH_2\underline{CH_3}$ and $CH_2(\underline{CH_2})_3CH_3$), 2.10~2.33(4H, m, 20-$\underline{CH_2}CH_3$ and $\underline{CH_2}(CH_2)_3CH_3$), 2.75 and 2.76(two 3H's, s, $NH^+(CH_3)_2$), 3.05~3.65(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.29(2H, s, 5-$H_2$), 5.38(2H, dd, J=11.0Hz, 17-H_2), 6.30~6.50(1H, br, 20-OH), 7.56(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.38(1H, t, J=5.5HZ, -$\underline{NH}CH_2CH_2NH^+$=), 10.15~10.32(1H, br, -$NHCH_2CH_2NH^+$=).

Example 27

(Preparation of 7-ethyl-17-cinnamoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride).

Using cinnamoyl chloride(538mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(447mg, 34.9% in yield) were obtained.
m.p. 140~143 °C (dec.)
IR ν (KBr)cm^{-1}; 3360, 2960, 2930, 1705, 1645, 1595, 1510, 1165.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.7ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (204mg, 96.2% in yield).
IR ν (KBr)cm^{-1}; 3340, 2670, 1700, 1650, 1595, 1510, 1165.
NMR(DMSO-d_6) δ ppm; 0.89(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.24(2H, q, 20-$\underline{CH_2}CH_3$), 2.73 and 2.74(two 3H's, s, $NH^+=(CH_3)_2$), 3.03 ~3.60(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.32(2H, s, 5-$H_2$), 5.54(2H, dd, J= 11.0Hz, 17-H_2), 6.32~6.58(1H, br, 20-OH), 6.62(1H, d, J=16.1Hz, CH=$\underline{CH}$Ph), 7.34 ~7.48(3H, m, Ph), 7.56(1H, s, 14-H), 7.64(1H, d, J=16.1Hz, CH=$\underline{CH}$Ph), 7.64~7.80 (3H, m, 10-H and Ph), 7.87(1H, t, 11-H), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H) 8.44 (1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+$=), 10.15~10.38(1H, br, -$NHCH_2CH_2\underline{NH}^+$=).

Example 28

(Preparation of 7-ethyl-17-phenylacetoxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using phenylacetyl chloride(499mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(233mg, 18.6% in yield) were obtained.
m.p. 108~114 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2960, 2930, 1725, 1645, 1590, 1510, 1450, 1140.

Hydrochloride

To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(3.0ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3300, 2670, 1720, 1650, 1595, 1510, 1140.
NMR(DMSO-d_6) δ ppm; 0.81(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1,33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.17(2H, q, 20-$\underline{CH_2}CH_3$), 2.74 and 2.75(two 3H's, s, $NH^+=(CH_3)_2$), 3.02 ~3.63(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+=$), 3.64(2H, s, $\underline{CH_2}Ph$), 5.30(2H, s, 5-H_2), 5.44(2H, dd, J=11.0Hz, 17-H_2), 6.32~6.50(1H, br, 20-OH), 7.20~7.41(5H, m, Ph), 7.56(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.38-(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+=$), 10.15~10.33(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 29

(Preparation of 7-ethyl-17-(4-phenylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 4-phenylbenzoyl chloride(700mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(214mg, 15.4% in yield) were obtained.
m.p. 197~201 °C (dec.)
IR ν (KBr)cm^{-1}; 3380, 3310, 2960, 2930, 1700, 1655, 1595, 1510, 1270, 1100.

Hydrochloride

To the suspension of free compound(160mg) in distilled water(10ml) 0.1N HCl(2.7ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3360, 2675, 1700, 1645, 1595, 1510, 1270, 1100.
NMR(DMSO-d_6) δ ppm; 0.91(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.17~2.34(2H, m, 20-$\underline{CH_2}CH_3$), 2.72 and 2.73(two 3H's, s, $\underline{NH^+}(CH_3)_2$), 3.03~3.58(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+=$), 5.35(2H, s, 5-$H_2$), 5.67(2H, dd, J=11.6Hz, 17-H_2), 6.41~6.53(1H, br, 20-OH), 7.36~7.56-(3H, m, Arom), 7.58 (1H, s, 14-H), 7.65~7.80(3H, m, 10-H and Arom), 7.81(2H, d, J=8, 1Hz, Arom), 7.87(1H, t, 11-H), 7.99(2H, d, Arom), 8.20(1H, d, 9-H), 8.30(1H, d, 12-H), 8.47(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+=$), 9.92~10.09(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 30

(Preparation of 7-ethyl-17-cyclohexanecarbonyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using cyclohexanecarbonyl chloride(474mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby pale yellow crystals of the title compound(378mg, 30.6% in yield) were obtained.
m.p. 119~123 °C (dec.)
IR ν (KBr)cm^{-1}; 3360, 2930, 2850, 1720, 1650, 1595, 1510, 1450, 1245, 1165.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(3.8ml) was added. All insoluble materials were filter d off and the filtrate was lyophilized to giv the hydrochlorid as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3350, 2930, 2675, 1715, 1645, 1595, 1510, 1450, 1170.
NMR(DMSO-d_6) δ ppm; 0.85(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.10~1.46(8H, m, 7-$CH_2\underline{CH_3}$ and cyclo-Hex), 1.50~1.90(5H, m, cyclo-Hex), 2.10~2.35(3H, m, 20-$\underline{CH_2}CH_3$ and cyclo-Hex), 2.75(6H, s, $NH^+(CH_3)_2$), 3.05~3.65(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2CH_2}NH^+$=), 5.29(2H, s, 5-$H_2$), 5.36(2H, dd, J=11.0Hz, 17-H_2), 6.41(1H, s, 20-OH), 7.56(1H, s, 14-H), 7.72(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.27(1H, d, 12-H), 8.38(1H, t, J=5.5Hz, -$N\underline{H}CH_2CH_2NH^+$=), 10.20~10.43(1H, br, -$NHCH_2CH_2N\underline{H}^+$=).

Example 31

(Preparation of 7-ethyl-17-stearoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using stearoyl chloride(978mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of the title compound(221mg, 14.0% in yield) was obtained.
IR ν ($CHCl_3$)cm^{-1}; 3400, 2920, 2850, 1725, 1650, 1595, 1510, 1455.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(3.0ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3340, 2915, 2845, 2680, 1720, 1645, 1590, 1510, 1460, 1165.
NMR(DMSO-d_6) δ ppm; 0.85(6H, t, 20-$CH_2\underline{CH_3}$ and $CH_2(CH_2)_{15}\underline{CH_3}$), 1.08~1.59 (33H, m, 7-$CH_2\underline{CH_3}$ and $CH_2(\underline{CH_2})_{15}CH_3$), 2.12~2.30(4H, m, 20-$\underline{CH_2}CH_3$ and $\underline{CH_2}(CH_2)_{15}CH_3$), 2.76(6H, s, $NH^+(CH_3)_2$), 3.03~3.63(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2CH_2}NH^+$=), 5.28(2H, s, 5-$H_2$), 5.37(2H, dd, J=11.0Hz, 17-H_2), 6.37(1H, s, 20-OH), 7.55(1H, s, 14-H), 7.72(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.37(1H, t, J=5.7HZ, -$N\underline{H}CH_2CH_2NH^+$=), 10.07~10.22(1H, br, -$NHCH_2CH_2N\underline{H}^+$=).

Example 32

(Preparation of 7-ethyl-17-oleoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using oleoyl chloride(972mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of solid title compound(202mg, 12.9% in yield) was obtained.
IR ν ($CHCl_3$)cm^{-1}; 3400, 2920, 2850, 1725, 1650, 1595, 1510, 1455.

Hydrochloride

To the suspension of free compound(163mg) in distilled water(20ml) 0.1N HCl(2.5ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a pale yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3340, 2920, 2835, 2685, 1720, 1645, 1595, 1510, 1455.
NMR(DMSO-d_6) δ ppm; 0.74~0.97(6H, m, 20-$CH_2\underline{CH_3}$ and $(CH_2)_7CH=CH(CH_2)_7\underline{CH_3}$), 1.11~2.05(29H;m, 7-$CH_2\underline{CH_3}$ and -$CH_2(CH_2)_6CH=CH(\underline{CH_2})_7CH_3$), 2.11~2.30(4H, m, 20-$\underline{CH_2}CH_3$ and -$COCH_2$-), 2.75(6H, s, $NH^+(CH_3)_2$), 3.03~3.62(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2CH_2}NH^+$=), 5.20~5.50(6H, m, 5-$H_2$, 17-$H_2$ and -CH=CH-), 6.38 (1H, s, 20-OH), 7.55(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.36(1H, t, J=5.5Hz, -$N\underline{H}CH_2CH_2NH^+$=), 10.03~10.21(1H, br, -$NHCH_2CH_2N\underline{H}^+$=).

Example 33

(Preparation of 7-ethyl-17-(4-methoxycarbonylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 4-methoxycarbonylbenzoyl chloride(542mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow solid of the title compound(279mg, 24.5% in yield) was obtained.
m.p. 192~194 °C (dec.)
IR ν (KBr)cm^{-1}; 3360, 2960, 2930, 1720, 1650, 1590, 1515, 1270, 1110, 1100.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(3.8ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (208mg, 98.1% in yield).
IR ν (KBr)cm^{-1}; 3360, 2675, 1710, 1650, 1595, 1510, 1270, 1115, 1100.
NMR(DMSO-d_6) δ ppm; 0.89(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.17~2.34(2H, m, 20-$\underline{CH_2}CH_3$), 2.72 and 2.73(two 3H's, s, $\overline{NH^+=(CH_3)_2}$), 3.03~3.61(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+=$), 3.88(3H, s, CO_2CH_3), 5.33(2H, s, 5-H_2), 5.70(2H, dd, J=11.0Hz, 17-H_2), 6.32~6.64(1H, br, $\overline{20\text{-}OH}$), 7.58(1H, s, 14-H), 7.74(1H, t, 10-H), 7.86(1H, t, 11-H), 8.03 and 8.07(two 2H's, s, $C_6\underline{H_4}$-CO_2CH_3), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.48(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+=$), 10.09~10.25(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 34

(Preparation of 7-ethyl-17-ethylsuccinyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using ethylsuccinyl chloride(449mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow solid of the title compound(253mg, 23.5% in yield) was obtained.
m.p. 120~121 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2970, 2930, 1730, 1645, 1590, 1155.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (200mg, 94.3% in yield).
IR ν (KBr)cm^{-1}; 3370, 2670, 2930, 2680, 1725, 1645, 1595, 1515, 1155.
NMR(DMSO-d_6) δ ppm; 0.86(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.19(3H, t, J=7.3Hz, -CO_2-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.3Hz, 7-$CH_2\underline{CH_3}$), 2.21(2H, q, 20-$\underline{CH_2}CH_3$), 2.54(4H, br, $\underline{CH_2CH_2}CO_2Et$), 2.75 and 2.77(two 3H's, s, $NH^+(CH_3)_2$), 3.05~3.72(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+=$), 4.07(2H, q, $CO_2\underline{CH_2}CH_3$), 5.29(2H, s, 5-H_2), 5.42 (2H, dd, J=10.6Hz, 17-H_2), 6.22~6.62(1H, br, 20-OH), 7.55(1H, s, 14-H), 7.72 (1H, t, 10-H), 7.85-(1H, t, 11-H), 8.18(1H, d, 9-H), 8.27(1H, d, 12-H), 8.38(1H, t, J=5.5Hz, -$NH\underline{CH_2}CH_2NH^+=$), 10.26~10.47(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 35

(Preparation of 7-ethyl-17-linoleoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using linoleoyl chloride(816mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of the title compound(280mg, 21.2% in yi ld) was obtained.
IR ν ($CHCl_3$)cm^{-1}; 3400, 2920, 2850, 1725, 1650, 1595, 1510, 1455.

Hydrochloride

To the suspension of free compound(250mg) in distilled water(25ml) 0.1N HCl(4.1ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3280, 2920, 2850, 2680, 1720, 1650, 1600, 1510, 1455, 1170.
NMR(DMSO-d_6) δ ppm; 0.73~0.95(6H, m, 20-$CH_2\underline{CH_3}$ and -$(CH_2)_7CH=CHCH_2CH=CH-(CH_2)_4\underline{CH_3}$), 1.06~1.62(23H, m, 7-$CH_2\underline{CH_3}$ and -$CH_2(\underline{CH_2})_6CH=CHCH_2CH=CH-(\underline{CH_2})_4CH_3$), 1.92~2.06(2H, m, $=CHCH_2\underline{CH}=$), 2.11~2.30(4H, m, 20-$\underline{CH_2}CH_3$ and -$COCH_2$-), 2.75(6H, s, $NH^+(CH_3)_2$), 3.00~3.63(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2CH_2NH^+=$), 5.18~5.50(8H, m, 5-H_2, 17-H_2 and -CH=CH-x2), 6.38(1H, s, 20-OH), 7.55(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.35(1H, t, J=5.8Hz, -$NHCH_2CH_2NH^+=$), 9.95~10.50(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 36

(Preparation of 7-ethyl-17-(4-chlorobutyryloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 4-chlorobutyryl chloride(385mg, 2.73mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(227mg, 22.0% in yield) were obtained.
m.p. ~199 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2960, 2930, 1725, 1645, 1590, 1510, 1455, 1210, 1185, 1140.
NMR($CDCl_3$) δ ppm; 1.09(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.35(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.03~2.15(2H, m, $CH_2\underline{CH_2}CH_2Cl$), 2.22(6H, s, -$N(CH_3)_2$), 2.25~2.57(6H, m, -$CH_2\underline{CH_2}N=$, $\underline{CH_2}CH_2CH_2Cl$ and 20-$\underline{CH_2}CH_3$), 3.01~3.48(4H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2CH_2,N=$), 3.61(2H, t, J=6.6Hz, $CH_2CH_2\underline{CH_2}Cl$), 5.11(2H, dd, J=18.7Hz, 5-H_2), 5.13(1H, s, 20-OH), 5.53(2H, dd, J=11.7Hz, 17-H_2), 7.35(1H, t, -$\underline{NH}CH_2CH_2N=$), 7.52~7.58(2H, m, 10-H and 14-H), 7.73(1H, m, 11-H), 7.93(1H, d, 9-H), 8.12(1H, d, 12-H).

Hydrochloride

To the suspension of free compound(150mg) in distilled water(10ml) 0.1N HCl(3.2ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3280, 2970, 2930, 2675, 1720, 1645, 1595, 1510, 1450.
NMR(DMSO-d_6) δ ppm; 0.86(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, 7-$CH_2\underline{CH_3}$),1.93~2.05(2H, m, $CH_2\underline{CH_2}CH_2Cl$), 2.21(2H, q, 20-$\underline{CH_2}CH_3$), 2.43(2H, t, J=7.3Hz, $\underline{CH_2}CH_2CH_2Cl$), 2.75 and 2.76(two 3H's, s, $NH^+(CH_3)_2$), 3.04~3.62(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2CH_2NH^+=$), 3.68(2H, t, J=6.6Hz, $CH_2CH_2\underline{CH_2}Cl$), 5.30(2H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.28(1H, d, 12-H), 8.39(1H, t, J=5.5Hz, -$NHCH_2CH_2NH^+=$), 10.11~10.27(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 37

(Preparation or 7-ethyl-17-((S)-(-)-N-(trifluorcacetyl)prolyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using (S)-(-)-N-(trifluoroacetyl)prolyl chloride (0.1M solution in dichloromethane, 18.2ml) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(200mg, 16.8% in yield) were obtained.
m.p. ~152 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2960, 2930, 1740, 1690, 1650, 1595, 1510, 1450, 1235, 1200, 1140.
NMR($CDCl_3$) δ ppm; 1.06(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.38(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 1.94~2.53(14H, m, -$N(CH_3)_2$, -$CH_2\underline{CH_2}N=$, Proline, and 20-$\underline{CH_2}CH_3$), 3.17 (2H, q, 7-$\underline{CH_2}CH_3$), 3.25~3.50(2H, m, $NHCH_2CH_2N=$), 3.65~3.95(2H, m, Proline), 4.37(1H, br, 20-OH), 4.42~4.53(1H, m, Proline), 5.19(2H, dd, J=18, 7Hz, 5-H_2), 5.68(1H, dd, J=11.0Hz, 17-H_2), 7.46(1H, t, J=5.0Hz, -$\underline{NH}CH_2CH_2N=$), 7.64(1H, t, 10-H), 7.74(1H, s, 14-H), 7.78(1H, t, 11-H), 8.08(1H, d, 9-H), 8.21(1H, d, 12-H).

Hydrochlorid

To the suspension of free compound(150mg) in distilled water(10ml) 0.1N HCl(2.7ml) was add d. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3370, 2965, 2675, 1735, 1685, 1650, 1595, 1510, 1455, 1230, 1205, 1145.
NMR(DMSO-d_6) δ ppm; 0.84(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 1.80~2.38(6H, m, Proline and 20-$\underline{CH_2}CH_3$), 2.75 and 2.76(two 3H's, s, $NH^+(CH_3)_2$), 3.01~3.82(8H, m, 7-$\underline{CH_2}CH_3$, $NHCH_2\underline{CH_2}N=$, and Proline), 4.43~ 4.62(1H, m, Proline), 5.29(2H, s, 5-H_2), 5.45(2H, dd, J=11.0Hz, 17-H_2), 6.30~ 6.70(1H, br, 20-OH), 7.58(1H, s, 14-H), 7.73(1H, t, 10-H), 7.85(1H, t, 11-H), 8.18 (1H, d, 9-H), 8.28(1H, d, 12-H). 8.40(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+=$), 10.20~ 10.44(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 38

(Preparation of 7-ethyl-17-(4-ethylbenzoyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 4-ethylbenzoyl chloride(460mg, 2.73mmol) as an acid chloride the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(763mg, 70.4% in yield) were obtained.
m.p. 140~144 °C (dec.)
IR ν (KBr)cm^{-1}; 3380, 2960, 2930, 1710, 1650, 1605, 1510, 1455, 1270, 1105.

Hydrochloride

To the suspension of free compound(300mg) in distilled water(20ml) 0.1N HCl(5.5ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (295mg, 92.6% in yield).
IR ν (KBr)cm^{-1}; 3360, 2670, 1700, 1645, 1595, 1510, 1275, 1105.
NMR(DMSO-d_6) δ ppm; 0.88(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.18(3H, t, J=7.7Hz, C_6H_4-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.16~2.35(2H, m, 20-$\underline{CH_2}CH_3$), 2.66 (2H, q, $C_6H_4\underline{CH_2}CH_3$), 2.70 and 2.72(two 3H's, s, $NH^+(CH_3)_2$), 3.00~3.59(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+=$), 5.33(2H, s, 5-$H_2$), 5.62(2H, dd, J=11.0Hz, 17-H_2), 6.36~6.57(1H, br, 20-OH), 7.33(2H, d, J=8.1Hz, Arom), 7.58(1H, s, 14-H), 7.73(1H, t, 10-H), 7.82(2H, d, Arom), 7.88(1H, t, 11-H), 8.19(1H, d, 9-H), 8.29(1H, d, 12-H), 8.44(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+=$), 10.02~10.22(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 39

(Preparation of 7-ethyl-17-(3-methylthiopropionyloxy)camptothecin-21-(2-dimethylamino)ethylamide and its hydrochloride)

Using 3-methylthiopropionyl chloride(378mg, 2.75mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(766mg, 74.4% in yield) were obtained.
m.p. 96~103 °C (dec.)
IR ν (KBr)cm^{-1}; 3350, 2960, 2930, 1730, 1645, 1590, 1510, 1455, 1250, 1215, 1185, 1140.

Hydrochloride

To the suspension of free compound (300mg) in distilled water(20ml) 0.1N HCl(5.8ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (314mg, 98.4%, in yield).
IR ν (KBr)cm^{-1}; 3355, 2675, 1725, 1645, 1595, 1515.
NMR(DMSO-d_6) δ ppm; 0.86(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.33(3H, t, 7-$CH_2\underline{CH_3}$), 2.07(3H, s, SCH_3), 2.22-(2H, q, J=7.0Hz, 20-$\underline{CH_2}CH_3$), 2.57 and 2.69(two 3H's, t, $COCH_2\underline{CH_2}SCH_3$), 2.75 and 2.76(two 3H's, s, $NH^+(CH_3)_2$), 3.03~3.68(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+=$), 5.29(2H, s, 5-$H_2$), 5.42(2H, dd, J=11.0Hz, 17-H_2), 6.25~6.58(1H, br, 20-OH), 7.55(1H, s, 14-H), 7.72(1H, t, 10-H), 7.85(1H, t, 11-H), 8.17(1H, d, 9-H), 8.27(1H, d, 12-H), 8.39(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+=$), 10.18~10.44(1H, br, -$NHCH_2CH_2\underline{NH^+}=$).

Example 40

(Preparation of 7-ethyl-17-(pivaloyloxy)camptothecin-21-)2-dimethylamino)ethylamide and its hydrochloride)

Using pivaloyl chloride(329mg, 2.75mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby yellow crystals of the title compound(362mg, 36.3% in yield) were obtained.
m.p. 202~204 °C (dec.)
IR ν (KBr)cm^{-1}; 3400, 3250, 2960, 1715, 1670, 1645, 1585, 1515, 1455, 1280, 1160.

Hydrochloride

To the suspension of free compound(200mg) in distilled water(20ml) 0.1N HCl(4.0ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the hydrochloride as a yellow amorphous solid (200mg, 93.9% in yield).
IR ν (KBr)cm^{-1}; 3360, 2960, 2685, 1710, 1645, 1595, 1510, 1280, 1155.
NMR(DMSO-d_6) δ ppm; 0.85(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.14(9H, s, $C(\underline{CH_3})_3$), 1.33 (3H, t, 7-$CH_2\underline{CH_3}$), 2.10(2H, m, 20-$\underline{CH_2}CH_3$), 2.75 and 2.76(two 3H's, s, $NH^+(CH_3)_2$), 3.05~3.67(6H, m, 7-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+$=), 5.29(2H, dd, J= 18.7Hz, 5-H_2), 5.35(2H, dd, J=11.0Hz, 17-H_2), 6.27~6.56(1H, br, 20-OH), 7.60 (1H, s, 14-H), 7.72(1H, t, 10-H), 7.84(1H, t, 11-H), 8.17(1H, d, 9-H), 8.27(1H, d, 12-H), 8.39(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+$=), 10.18~10.40(1H, br, -$NHCH_2CH_2\underline{NH^+}$=).

Example 41

(Preparation of 7-ethyl-17-phenoxyacetoxycamptothecin-21-(2-dimethylamino)ethylamide)

Using phenoxyacetyl chloride(551mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 14, whereby a yellow syrup of the title compound(161mg) was obtained, which was crystallized from $CHCl_3$-n-hexane to give yellow crystals-(62mg, 4.8% in yield).
m.p. 112~117 °C (dec.)
IR ν (KBr)cm^{-1}; 3360, 2960, 2920, 1750, 1650, 1595.
NMR($CDCl_3$) δ ppm; 1.07(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.35(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.19(6H, s, N-$(CH_3)_2$), 2.22~2.57(4H, m, -$CH_2\underline{CH_2}N$= and 20-$\underline{CH_2}CH_3$), 3.10(2H, q, 7-$\underline{CH_2}CH_3$), 3.24~3.46(2H, m, $NHCH_2CH_2N$=), 4.64(2H, s, $CO\underline{CH_2}OPh$), 4.93~5.28(1H, br, 20-OH), 5.09(2H, dd, J=18.7Hz, 5-H_2), 5.65-(1H, dd, J=11.4Hz, 17-H_2), 6.82~7.03(3H, m, OPh), 7.21~7.31(2H, m, OPh), 7.36(1H, t, J=5.5Hz, $NHCH_2CH_2N$=), 7.52(1H, t, 10-H), 7.55(1H, s, 14-H), 7.72(1H, t, 11-H), 7.88(1H, d, 9-H), 8.09(1H, d, 12-H).

Example 42

(Preparation of 7-ethyl-17-(3-ethoxypropionyloxy)camptothecin-21-(2-dimethylamino)ethylamide)

To the ice-cooled solution of 3-ethoxypropionic acid (323mg, 2.73 mmol) in dichloromethane, N,N'-dicyclohexylcarbodiimide(DCC, 846mg, 4.10mmol) was added and the reaction mixture was stirred for 0.5 hour. After adding the solution of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylamino)ethylamide(1.00g, 2.15mmol) in dichloromethane(10ml) and 4-N,N-dimethylaminopyridine(100mg, 0.82mmol), the reaction mixture was stirred for an hour under ice-cooling and then for an hour at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residual materials were purified through silica gel column chromatography with $CHCl_3$-MeOH as an eluent and crystallized from $CHCl_3$-n-hexane to give yellow crystals of the title compound (50mg, 4.9% in yield).
m.p. 119~123 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2960, 2930, 2860, 1730, 1645, 1590, 1515, 1455, 1180.
NMR($CDCl_3$) δ ppm; 1.07(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.17(3H, t, J=7.0Hz, $OCH_2\underline{CH_3}$), 1.36(3H, t, J=7.7Hz, 7-$CH_2\underline{CH_3}$), 2.23(6H, s, -$N(CH_3)_2$), 2.24~2.53(4H, m, -$CH_2\underline{CH_2}N$= and 20-$\underline{CH_2}CH_3$), 2.61(2H, t, J=6.2Hz, -$CO\underline{CH_2}\underline{CH_2}O$), 3.02~3.58(6H, m, 7-$\underline{CH_2}CH_3$, -$NH\underline{CH_2}CH_2N$= and $OCH_2\underline{CH_3}$), 3.62~3.80(2H, m, -$COCH_2\underline{CH_2}O$), 4.80~ 5.10(1H, br, 20-OH), 5.13(2H, dd, J=18.7Hz, 5-H_2), 5.55(2H, dd, J=11.4Hz, 17-H_2), 7.38(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2N$=), 7.56(1H, t, 10-H), 7.60(1H, s, 14-H), 7.74(1H, t, 11-H), 7.96(1H, d, 9-H), 8.14(1H, d, 12-H).

Example 43

(Preparation of 7-ethyl-17-(N-tert-butoxycarbonyl-L-alanyloxy)campto thecin-21-(2-dimethylamino)-ethylamide)

To the salt-ice-cooled solution of tert-butoxycarbonyl-L-alanine (517 mg, 2.73mmol) in THF(15ml), triethylamine(0.38ml, 2.73mmol) and iso-butyl chloroformate(373mg, 2.73mmol) were added and the reaction mixture was stirred for 5 minutes. After adding the solution of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylamino)ethylamide(1.00g, 2.15mmol) in THF(15ml) and 4-N,N-dimethylaminopyridine(100mg, 0.82 mmol), the reaction mixture was stirred for an hour under ice-cooling and then for 3 hours at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residual materials were dissolved in $CHCl_3$ and washed with a saturated aqueous solution of $NaHCO_3$ and with a saturated aqueous slution of NaCl. The organic phase was separated, dried with anhydrous $MgSO_4$, and then evaporated to dryness under reduced pressure. The residual materials were purified through silica gel column chromatography with $CHCl_3$-MeOH as an eluent and crystallized from $CHCl_3$-n-hexane to give pale yellow crystals of the title compound(91mg, 7.9% in yield).

m.p. ~130 °C (dec.)

IR ν (KBr)cm^{-1}; 3340, 2970, 2930, 1735, 1705, 1650, 1595, 1510, 1450, 1160.

NMR($CDCl_3$) δ ppm; 1.07(3H, t, J=7.3Hz, 20-CH_3CH_3), 1.28~1.48(15H, m, 7-CH_2CH_3, -$CH(CH_3)$- and -$C(CH_3)_3$), 2.20~2.53(4H, m, -CH_2CH_2N= and 20-CH_2CH_3), 2.25(6H, s, -$N(CH_3)_2$), 3.15(2H, q, 7-CH_2CH_3), 3.27~3.50(2H, m, -$NHCH_2CH_2N$=), 4.13~4.30(1H, m, $COCH(CH_3)NHCO$), 4.63~5.04(1H, br, 20-OH), 5.17-(2H, dd, J= 18.7Hz, 5-H_2), 5.28(1H, d, J=6.6Hz, $COCH(CH_3)NHCO$), 5.62(2H, dd, J=11.0Hz, 17-H_2), 7.46-(1H, br-t, -$NHCH_2CH_2N$=), 7.61(1H, t, 10-H), 7.68(1H, s, 14-H), 7.76(1H, t, 11-H), 8.04(1H, d, 9-H), 8.18(1H, d, 12-H).

Example 44

(Preparation of 7-ethyl-17-nicotinoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its dihydrochloride

To the ice-cooled DMF solution(10ml) of 7-ethyl-17-hydroxycamptothecin-21-(2-dimethylamino)-ethylamide(1.00g, 2.15mmol), the DMF solution (10ml) of nicotinoyl chloride hydrochloride(575mg, 3.23mmol) was added in the presence of 4-N,N-dimethylaminopyridine(100mg, 0.82mmol). The reaction mixture was stirred for an hour under ice-cooling and for 0.5 hours at room temperature. Then the reaction mixture was evaporated to dryness under reduced pressure, and the residual materials were dissolved in $CHCl_3$ and washed with a saturated aqueous solution of $NaHCO_3$ and with a saturated aqueous solution of NaCl. The organic phase was separated, dried with anhydrous Na_2SO_4, then evaporated to dryness under reduced pressure. The resulting materials were purified through silica gel column chromatography with $CHCl_3$-MeOH as an eluent and crystallized from $CHCl_3$-n-hexane to give pale yellow crystals of the title compound (157 mg, 12.8% in yield).

m.p. ~162 °C (dec.)

IR ν (KBr)cm^{-1}; 3360, 2970, 2930, 1715, 1645, 1590, 1510, 1275, 1110.

Dihydrochloride

To the suspension of free compound(120mg) in distilled water(20ml) 0.1N HCl(4.6ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the dihydrochloride as a yellow amorphous solid (126mg, 93.3% in yield).

IR ν (KBr)cm^{-1}; 3375, 2680, 1730, 1645, 1590, 1520, 1460, 1290, 1130.

NMR(DMSO-d_6) δ ppm; 0.89(3H, t, J=7.3Hz, 20-CH_2CH_3), 1.32(3H, t, J=7.7Hz, 7-CH_2CH_3), 2.13~2.38(2H, m, 20-CH_2CH_3), 2.72 and 2.73(two 3H's, s, $NH^+(CH_3)_2$), 3.02~3.64(6H, m, 7-CH_2CH_3 and $NHCH_2CH_2NH^+$=), 5.32(2H, s, 5-H_2), 5.73(2H, dd, J=11.0Hz, 17-H_2), 6.30~6.75(1H, br, 20-OH), 7.58(1H, s, 14-H), 7.60~7.78 (2H, m, 10-H and Py), 7.86(1H, t, 11-H). 8.20(1H, d, 9-H), 8.24~8.37(2H, m, 12-H and Py), 8.49(1H, t, J=5.5Hz, -$NHCH_2CH_2NH^+$=), 8.84(1H, dd, J=1.8 and 5.1Hz, Py), 9.06(1H, d, J=1.5Hz, Py), 10.22~10.42(1H, br, -$NHCH_2CH_2NH^+$=).

Example 45

(Preparation of 7-ethyl-17-iso-nicotinoyloxycamptothecin-21-(2-dimethylamino)ethylamide and its dihydrochloride)

Using iso-nicotinoyl chloride hydrochloride(575mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 44, whereby yellow crystals of the title compound(445mg, 36.3% yield) were obtained.
m.p. 168~171 °C (dec.)
IR ν (KBr)cm^{-1}; 3350, 2960, 2930, 1720, 1645, 1595, 1510, 1275, 1120.

Dihydrochloride

To the suspension of free compound(200mg) in distilled water(15ml) 0.1N HCl(7.7ml) was added. All insoluble materials were filtered off and the filtrate was lyophilized to give the dihydrochloride as a yellow amorphous solid in quantitative yield.
IR ν (KBr)cm^{-1}; 3360, 2675, 1725, 1645, 1590, 1510, 1280, 1120.
NMR(DMSO-d_6) δ ppm; 0.89(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.32(3H, t, J=7.3Hz, 7-$CH_2\underline{CH_3}$), 2.14~2.38(2H, m, 20-$\underline{CH_2}CH_3$), 2.72 and 2.73(two 3H's, s, $NH^+(CH_3)_2$), 3.02~3.63(6H, m, 7-$\underline{CH_2}CH_3$ and $NH\underline{CH_2}\underline{CH_2}NH^+$=), 5.33(2H, s, 5-$H_2$), 5.77(2H, dd, J=11.0Hz, 17-H_2), 6.26~6.80(1H, br, 20-OH), 7.58(1H, s, 14-H), 7.74(1H, t, 10-H), 7.87(1H, t, 11-H), 7.91(2H, d, J=5.1Hz, Py), 8.21(1H, d, 9-H), 8.30(2H, d, 12-H), 8.51(1H, t, J=5.5Hz, -$\underline{NH}CH_2CH_2NH^+$=), 8.87(2H, d, Py), 10.29~10.47(1H, br, -$NHCH_2CH_2\underline{NH^+}$=).

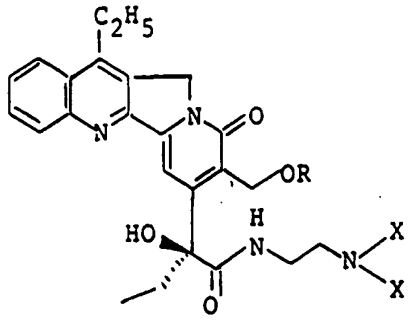
Example 46

(Preparation of 7-ethyl-17-picolinoyloxycamptothecin-21-(2-dimethylamino)ethylamide)

Using picolinoyl chloride hydrochloride(575mg, 3.23mmol) as an acid chloride, the reaction followed by the after-treatment was carried out in the same manner as described in example 44, whereby the yellow crystals of the title compound(23mg, 1.9% in yield) were obtained.
m.p. ~154 °C (dec.)
IR ν (KBr)cm^{-1}; 3370, 2960, 2930, 1715, 1650, 1595, 1510, 1455, 1305, 1285, 1245, 1130.
NMR($CDCl_3$) δ ppm; 1.06(3H, t, J=7.3Hz, 20-$CH_2\underline{CH_3}$), 1.38(3H, t, J=7.3Hz, 7-$CH_2\underline{CH_3}$), 2.15~2.55(4H, m, 20-$\underline{CH_2}CH_3$ and $NHCH_2\underline{CH_2}NH^+$=), 2.23(3H, s, $\underline{NH}(CH_3)_2$), 3.16(2H, q, 7-$\underline{CH_2}CH_3$), 3.26~3.50(2H, m, $NH\underline{CH_2}CH_2NH^+$=), 5.07~5.53(1H, br, 20-OH), 5.19(2H, s, 5-H_2), 5.87(2H, dd, J=11.4Hz, 17-H_2), 7.50(1H, br, -NH-), 7.62(1H, t, 10-H), 7.65(1H, s, 14-H), 7.74~7.85(2H, m, 11-H and Py), 8.06(1H, d,9-H), 8.13~8.23-(2H, m, 12H and Py), 8.65~8.70(1H, m, Py).

Claims

1. Camptothecin derivatives of the general formula:



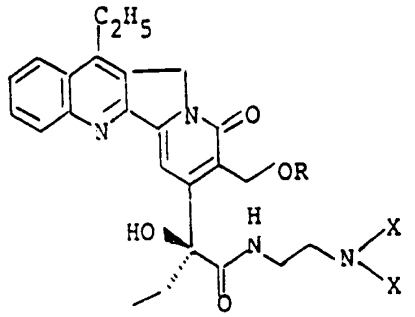
(I)

wherein
X is a C_1-C_6 alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or

branched unsubstituted C_1-C_{18} alkyl group; a C_1-C_6 alkyl group substituted by a halogen atom or a C_1-C_6 alkylthio, amino, acylamino, hydroxyl, C_1-C_6 alkoxy, phenyloxy or naphthyloxy or C_1-C_6 alkoxycarbonyl group; a C_3-C_{19} alyenyl, C_3-C_{19} alkynyl or C_3-C_8 cycloalkyl group; a C_3-C_8 cycloalkyl group substituted by an acylamino-C_1-C_6 alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, phenyl or C_1-C_6 alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thienyl group,

wherein the acyl moiety in the acylamino and N-acylpyrrolidyl groups stands for a residue of an acid preferably selected from aliphatic and aromatic carboxylic acids including amino acids, aliphatic and aromatic sulfonic acids, and halogen- or hydroxy-substituted derivatives thereof, and their acid addition salts formed at the amino group and quaternary ammonium salts.

2. A process for the preparation of camptothecin derivatives of the general formula:



(I)

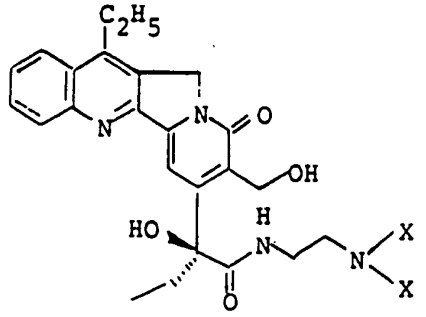
wherein

X is a C_1-C_6 alkyl group, and R is a hydrogen atom or the grouping -COY where Y is a linear or branched unsubstituted C_1-C_{18} alkyl group; a C_1-C_6 alkyl group substituted by a halogen atom or a C_1-C_6 alkylthio, amino, acylamino, hydroxyl, C_1-C_6 alkoxy, phenyloxy or napthyloxy or C_1-C_6 alkoxycarbonyl group; a C_3-C_{19} alkenyl, C_3-C_{19} alkynyl or C_3-C_8 cycloalkyl group; a C_3-C_8 cycloalkyl group substituted by an acylamino C_1-C_6 alkyl group; an N-acylpyrrolidyl group; a phenyl group; a phenyl group substituted by a halogen atom or a trifluoromethyl, nitro, amino, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, phenyl or C_1-C_6 alkoxy; a cinnamyl group; a benzyl group; a naphthyl group; a pyridyl group; a furyl group; or a thienyl group,

wherein the acyl moiety in the acylamino and N-acylpyrrolidyl groups stands for a residue of an acid preferably selected from aliphatic and aromatic carboxylic acids including amino acids, aliphatic and aromatic sulfonic acids, and halogen- or hydroxy-substituted derivatives thereof, and their physiologically acceptable acid-addition salts at the amino group, which comprises treating 7-ethylcamptothecin with an ethylenediamine derivative of the general formula:

$H_2N\text{-}CH_2CH_2\text{-}NX_2$ (VI)

wherein X has the same meaning as given above, to form a 7-ethyl-17-hydroxymethylcamptothecin-21-(2-dialkylamino)ethylamide of the general formula:



(V)

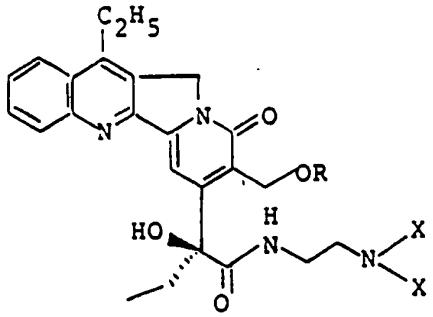
wherein X has the same meaning as given above, and if necessary, acylating the resultant compound of the general formula (V) with a compound of the general formula:

Z-COY (VII)

wherein Y has the same meaning as given above and Z is a hydroxyl group, a halogen atom or the grouping -O-COY, and if desired, converting the resultant compound of the general formula (I) into its physiologically acceptable acid addition salt or quaternary ammonium salt or vice versa.

Patentansprüche

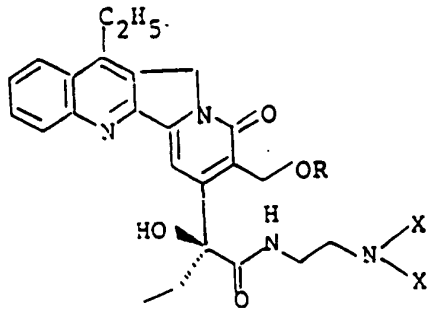
1. Camptothecinderivate der allgemeinen Formel



(I)

in der
X einen C_1-C_6-Alkylrest bedeutet, und R ein Wasserstoffatom oder den Rest -COY darstellt, in dem Y einen unverzweigten oder verzweigten unsubstituierten C_1-C_{18}-Alkylrest; einen C_1-C_6-Alkylrest, der mit einem Halogenatom oder einem C_1-C_6-Alkylthiorest, einer Aminogruppe, einem Acylaminorest, einer Hydroxylgruppe, einem C_1-C_6-Alkoxyrest, einer Phenoxy- oder Naphthyloxygruppe oder einem C_1-C_6-Alkoxycarbonylrest substituiert ist; einen C_3-C_{19}-Alkenyl-, C_3-C_{19}-Alkinyl- oder C_3-C_8-Cycloalkylrest; einen C_3-C_8-Cycloalkylrest, der mit einem Acylamino-C_1-C_6-alkylrest substituiert ist; einen N-Acylpyrrolidylrest; eine Phenylgruppe; eine mit einem Halogenatom oder einer Trifluormethyl-, Nitro- oder Aminogruppe, einem C_1-C_6-Alkoxycarbonyl- oder C_1-C_6-Alkylrest oder einer Phenylgruppe oder einem C_1-C_6-Alkoxyrest substituierte Phenylgruppe; eine Cinnamylgruppe; eine Benzylgruppe; eine Naphthylgruppe; eine Pyridylgruppe; eine Furylgruppe; oder eine Thienylgruppe; bedeutet, wobei der Acylanteil der Acylamino- und N-Acylpyrrolidylreste den Rest einer Säure bedeutet, die vorzugsweise ausgewählt ist aus aliphatischen und aromatischen Carbonsäuren, einschließlich Aminosäuren, aliphatischen und aromatischen Sulfonsäur n und deren halogen- oder hydroxysubstituierten Derivaten, und deren an der Aminogruppe gebildete Säureadditionssalze und quartär Ammoniumsalz .

2. Verfahren zur Herstellung von Camptothecinderivaten der allgemeinen Formel

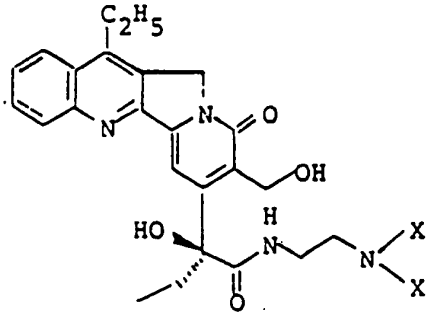


(I)

in der
X einen C_1-C_6-Alkylrest bedeutet, und R ein Wasserstoffatom oder den Rest -COY darstellt, in dem Y einen unverzweigten oder verzweigten unsubstituierten C_1-C_{18}-Alkylrest; einen C_1-C_6-Alkylrest, der mit einem Halogenatom oder einem C_1-C_6-Alkylthiorest, einer Aminogruppe, einem Acylaminorest, einer Hydroxylgruppe, einem C_1-C_6-Alkoxyrest, einer Phenoxy- oder Naphthyloxygruppe oder einem C_1-C_6-Alkoxycarbonylrest substituiert ist; einen C_3-C_{19}-Alkenyl-, C_3-C_{19}-Alkinyl- oder C_3-C_8-Cycloalkylrest; einen C_3-C_8-Cycloalkylrest, der mit einem Acylamino-C_1-C_6-alkylrest substituiert ist; einen N-Acylpyrrolidylrest; eine Phenylgruppe; eine mit einem Halogenatom oder einer Trifluormethyl-, Nitro- oder Aminogruppe, einem C_1-C_6-Alkoxycarbonyl- oder C_1-C_6-Alkylrest oder einer Phenylgruppe oder einem C_1-C_6-Alkoxyrest substituierte Phenylgruppe; eine Cinnamylgruppe; eine Benzylgruppe; eine Naphthylgruppe; eine Pyridylgruppe; eine Furylgruppe; oder eine Thienylgruppe; bedeutet, wobei der Acylanteil der Acylamino- und N-Acylpyrrolidylreste den Rest einer Säure bedeutet, die vorzugsweise ausgewählt ist aus aliphatischen und aromatischen Carbonsäuren, einschließlich Aminosäuren, aliphatischen und aromatischen Sulfonsäuren und den halogen- oder hydroxysubstituierten Derivaten davon, und ihren physiologisch verträglichen, mit der Aminogruppe gebildeten Säureadditionssalzen, umfassend die Umsetzung von 7-Ethylcamptothecin mit einem Ethylendiaminderivat der allgemeinen Formel:

$H_2N\text{-}CH_2CH_2\text{-}NX_2$ (VI)

in der X die vorstehend angegebene Bedeutung hat, zu einem 7-Ethyl-17-hydroxymethylcamptothecin-21-(2-dialkylamino)ethylamidder allgemeinen Formel:



(V)

in der X die vorstehend angegebene Bedeutung hat, und falls erforderlich, das Acylieren der erhaltenen Verbindung der allgemeinen Formel (V) mit einer Verbindung der allgemeinen Formel

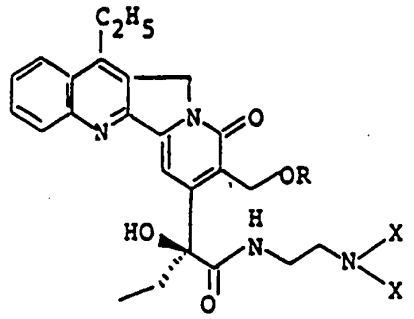
Z-COY (VII)

in der Y die vorstehend angegebene Bedeutung hat und Z eine Hydroxylgruppe, ein Halogenatom oder

den Rest -O-COY bedeutet, und falls gewünscht, das Umwandeln der erhaltenen Verbindung der allgemeinen Formel (I) in ihr physiologisch verträgliches Säureadditionssalz oder quartäres Ammoniumsalz oder umgekehrt.

Revendications

1. Dérivés de camptothécine de formule générale :

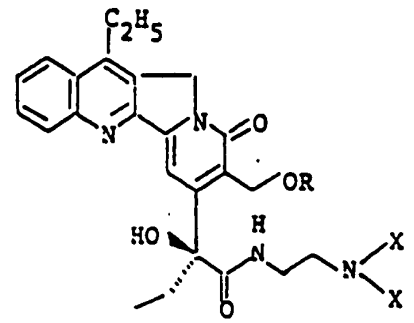


(I)

dans laquelle

X est un groupe alkyle en C_1-C_6 et R est un atome d'hydrogène ou le groupement -COY, où Y est un groupe alkyle en C_1-C_{18} non substitué, linéaire ou ramifié ; un groupe alkyle en C_1-C_6 substitué par un atome d'halogène ou un groupe alkylthio en C_1-C_6, amino, acylamino, hydroxyle, alcoxy en C_1-C_6, phényloxy, naphtyloxy ou (alcoxy en C_1-C_6)carbonyle ; un groupe alcényle en C_3-C_{19}, alcynyle en C_3-C_{19} ou cycloalkyle en C_3-C_8 ; un groupe cycloalkyle en C_3-C_8 substitué par un groupe acylaminoalkyle en C_1-C_6 ; un groupe N-acylpyrrolidyle ; un groupe phényle ; un groupe phényle substitué par un atome d'halogène ou un groupe trifluorométhyle, nitro, amino, (alcoxy en C_1-C_6)carbonyle, alkyle en C_1-C_6, phényle ou alcoxy en C_1-C_6 ; un groupe cinnamyle ; un groupe benzyle ; un groupe naphtyle ; un groupe pyridyle ; un groupe furyle ; ou un groupe thiényle,
où le fragment acyle dans les groupes acylamino et N-acylpyrrolidyle est un reste d'un acide choisi de préférence parmi les acides carboxyliques aliphatiques et aromatiques, y compris les amino-acides, les acides sulfoniques aliphatiques et aromatiques et leurs dérivés halogéno- ou hydroxy-substitués, et leurs sels d'addition d'acides formés sur le groupe amino et leurs sels d'ammonium quaternaire.

2. Un procédé pour la préparation de dérivés de camptothécine de formule générale :



(I)

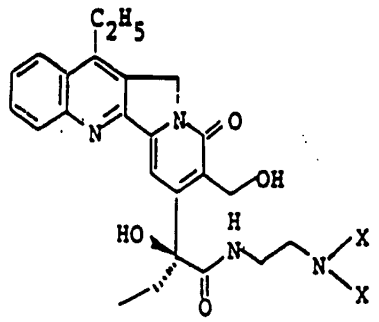
dans laquelle

X est un groupe alkyle en C_1-C_6 et R est un atome d'hydrogène ou le groupement -COY, où Y est un groupe alkyle n C_1-C_{18} non substitué, linéaire ou ramifié ; un group alkyle en C_1-C_6 substitué par un atom d'halogène ou un groupe alkylthio en C_1-C_6, amino, acylamino, hydroxyle, alcoxy en C_1-C_6, phényloxy, naphtyloxy ou (alcoxy en C_1-C_6)carbonyle ; un groupe alcényle en C_3-C_{19}, alcynyl en C_3-C_{19} ou cycloalkyle en C_3-C_8 ; un group cycloalkyle en C_3-C_8 substitué par un groupe acylaminoalkyle en C_1-C_6 ; un groupe N-acylpyrrolidyle ; un groupe phényle ; un groupe phényle substitué par

un atome d'halogène ou un groupe trifluorométhyle, nitro, amino, (alcoxy en C_1-C_6)carbonyl , alkyle en C_1-C_6, phényl ou alcoxy en C_1-C_6 ; un group cinnamyle ; un groupe benzyl ; un groupe naphtyle ; un groupe pyridyle ; un groupe furyle ; ou un groupe thiényle,
où le fragment acyle dans les groupes acylamino et N-acylpyrrolidyle est un reste d'un acide choisi de préférence parmi les acides carboxyliques aliphatiques et aromatiques, y compris les amino-acides, les acides sulfoniques aliphatiques et aromatiques et leurs dérivés halogéno- ou hydroxy-substitués, et leurs sels d'addition d'acides physiologiquement acceptables formés sur le groupe amino, qui comprend le traitement de la 7-éthylcamptothécine avec un dérivé d'éthylènediamine de formule générale :

$H_2N\text{-}CH_2CH_2\text{-}NX_2$ (VI)

dans laquelle X a la même signification que ci-dessus, pour former un 7-éthyl-17-hydroxyméthylcamptothécine-21-(2-dialkylamino)éthylamidede formule générale :



(V)

dans laquelle X a la même signification que ci-dessus, et, le cas échéant, l'acylation du composé obtenu de formule générale (V) avec un composé de formule générale :

Z-COY (VII)

dans laquelle Y a la même signification que ci-dessus et Z est un groupe hydroxyle, un atome d'halogène ou le groupement -O-COY, et, si on le désire, la conversion du composé obtenu de formule générale (I) en son sel d'addition d'acide physiologiquement acceptable ou son sel d'ammonium quaternaire ou vice et versa.